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Treatment patterns in inpatient depression care

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latent class analysis, complex interventions, inpatient treatment, depressive disorders, health services

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Abstract

This study aimed to identify latent patterns of treatment combinations in inpatient depression care. A secondary analysis of routinely collected data on inpatient depression treatment from 2133 patients was conducted. Exploratory latent class modeling was used to identify distinct classes of treatment combinations based on antidepressant medication, psychotherapeutic interventions, and additional treatments. The classes were compared with regard to patient characteristics and treatment outcomes. Eight different classes of inpatient treatment combinations could be identified: 22.8% of the patients were treated with a combination labelled "standard modern antidepressants", 14.6% with "standard tricyclic antidepressants", 12.2% with "high intensity innovative strategies", 12.1% with "standard selective-reuptake-inhibitors", and 11.6% with "low intensity", 9.6% with "somatic", 8.8% with "high intensity traditional", and 8.3% with "high intensity psychosocial" care, respectively. Patients treated with different patterns of interventions differed statistically significantly regarding demographic and clinical characteristics. Responder rates ranged from 68.4% to 86.6% across treatment classes. The presented attempt of empirical modeling of a complex multifactorial intervention by means of latent class analysis proved to be a promising way of capturing the complexity of routine inpatient depression treatment. The identified classes of treatment combinations may provide relevant information for a re-evaluation and improvement of inpatient depression treatment strategies. *Copyright © 2015 John Wiley & Sons, Ltd.*

Introduction

Depressive disorders constitute one of the most prevalent and disabling diseases (Ferrari *et al.*, 2013; Murray and Lopez, 1996). Similarly to other Western countries, lifetime prevalence rate for a diagnosis of unipolar depression is 11.6% in Germany, and 8.1% of the population has been suffering from depressive symptoms within the last four weeks (Busch *et al.*, 2013; Reeves *et al.*, 2011). Approximately 25% of all inpatient treatments and 40% to 60% of all outpatient psychotherapies in Germany are due to depressive disorders (Schulz *et al.*, 2006). The direct costs of depression amounted to 5.2 billion Euros in 2008, and 210,000 work years were lost in the same year (Statistisches Bundesamt, 2008). Various promising pharmacological, psychotherapeutic and combined treatment options for depressive disorders exist and findings on their effectiveness are summarized in current clinical practice

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guidelines (American Psychiatric Association, 2010; Härter *et al.*, 2008; National Institute for Health and Clinical Excellence [NICE], 2009). Yet, a discrepancy between empirical evidence and routine clinical practice is often reported (Petersen *et al.*, 2002).

In comparison to other European countries and the United States, a high proportion of depressed patients receive inpatient treatment in Germany (Hölzel *et al.*, 2011). The duration of inpatient treatment for depressive disorders is rather long in comparison to other mental disorders (Bender *et al.*, 2007). Although first results indicate that routine inpatient depression care can lead to promising outcomes (Härter *et al.*, 2004), not all patients achieve complete remission during inpatient treatment (Bottlender and Möller, 2005; Hölzel *et al.*, 2010; Seemüller *et al.*, 2010). Insufficient treatment may lead to the persistence of depressive symptoms and an increased risk of chronification (Fava *et al.*, 1994). Therefore, further improvement of (inpatient) depression treatment is strongly necessary.

In routine inpatient care patients often receive more than one pharmacological agent at the same time. It is a common strategy, especially in acute treatments, to combine antidepressants with antipsychotics, sedative-hypnotics, or other antidepressants (Barbui *et al.*, 2005; Bauer *et al.*, 2008; de la Gándara *et al.*, 2005; Härter *et al.*, 2004; Mojtabai and Olfson, 2010). Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are the most frequently applied antidepressant medications in Germany, and at least one out of five patients receive more than one antidepressant simultaneously (Voderholzer *et al.*, 2008). The medication regimen is changed during inpatient depression treatment for every third patient (Härter *et al.*, 2004). In addition to pharmacological treatments, most hospitals offer a wide range of further inpatient treatments such as psychotherapy, somatic therapies, or physical exercise programs (Wolfersdorf, 2003; Wolfersdorf and Müller, 2007). These interventions are frequently combined (Wolfersdorf *et al.*, 2001). Because of the high number of components used in inpatient depression treatment that may act both independently and interdependently, routine inpatient care can be considered as a complex intervention (Campbell *et al.*, 2007). Its evaluation is therefore facing practical and methodological challenges, such as differentiating effective from ineffective treatment components (Craig *et al.*, 2008).

First results concerning the effectiveness of different combinations of interventions in inpatient care showed that adding psychotherapy to a pharmacological treatment can enhance outcome especially for patients with mental comorbidity (Hölzel *et al.*, 2010). Other findings suggest that a greater number of concurrent antidepressant medications do not necessarily lead to an increased efficacy (Glezer *et al.*, 2009), but the type of received pharmacological treatment during inpatient stay was associated with the length of inpatient stay (Seemüller *et al.*, 2010).

Yet, even complex analytical approaches in previous studies have often failed to account for the diversity of care. For example, traditional variable-centered statistical methods are unable of handling numerous complex interactions as they appear in inpatient treatment. A novel person-centered approach that may be able to represent the complexity of interventions administered in inpatient depression treatment by generating probability-based classes of treatment combinations is *latent class modeling* (Marcoulides and Moustaki, 2002).

The objective of this study was therefore to capture the complexity of routine inpatient depression treatment descriptively by applying latent class modeling. The primary aim was to identify latent (i.e. not directly observable) classes of intervention combinations in inpatient depression treatment. Additionally, the study examined whether patients belonging to different classes (i.e. receiving different treatment combinations) differ with regard to demographic and clinical characteristics, and whether the received intervention combinations were associated with different treatment outcomes. Thereby, this study may help to close the gap between research on interventions, usually testing monotherapies up to three-fold combinations, and routine care, as well as to outline insights for further improvement of inpatient depression treatment (Pfaff *et al.*, 2009a, 2009b).

Methods

A secondary analysis based on data from a study of the German Research Network on Depression was conducted. Within this multicenter study, quality of inpatient treatment was assessed in 10 psychiatric-psychotherapeutic hospitals (for a more detailed description of the study, see previous publications [Schneider *et al.*, 2005; Sitta *et al.*, 2005]). The study resulted in one of the largest and most extensive routinely collected datasets on inpatient depression care in German psychiatric settings including structure-, process-, and outcome-related data.

Patient sample

The studied population included adult patients with a depressive disorder meeting criteria for one of the following International Classification of Disease, 10th revision (ICD-10) (World Health Organization, 1993) diagnoses: bipolar

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depressive episode (F31.3–F31.5), unipolar depressive episode (F32.0–F32.2), recurrent depressive episode (F33.0–F33.9), dysthymia (F34.1), other chronic depressive disorders (F33.8–F33.9), other affective disorders (F38–F39), and adjustment disorders with depressive symptoms (F43.20–F43.21). All patients who received a minimum of three days of inpatient treatment in one of the cooperating hospitals were included.

Hospital sample

To increase generalizability of the findings and to be able to investigate the effects of structural heterogeneity, hospitals in different regions, of various type, and size were chosen. The hospital sample consisted of two university hospitals, five state psychiatric hospitals, and three general hospitals. In half of the participating hospitals a quality assurance intervention was introduced as part of the primary study. The intervention aimed to improve treatment processes and included training in current clinical practice guidelines and introduction of quality circles. In all hospitals, different groups of patients were included in the study before (baseline) and after (follow-up) the hospital-level quality assurance intervention.

Data collection

Data were collected during the recruitment phase between December 2001 and February 2003. Within the first three days of admission, each patient was asked to rate his or her level of depression. The responsible therapist documented the patient's demographic characteristics, history of depression and psychopathology, rated the patient's level of depression and recorded treatment characteristics (e.g. diagnostic and therapeutic procedures) during inpatient treatment by means of a documentation system (BADO). At discharge, patients rated their level of depression and satisfaction with the received treatment. Therapists rated the patients' level of depression and documented the discharge process (e.g. subsequent treatment plans, changes in job situation). In order to take the complexity of treatment into account, structure, process, and outcome quality aspects were assessed (Donabedian, 1966). Data for each patient were anonymized and sent to the study center for statistical analysis. Since the analysis of routine data for quality assurance reasons is a legal obligation to German health care laws, it was not necessary to obtain additional informed consent from every patient. Ethical principles of the Declaration of Helsinki (last updated in 2013) were followed throughout the study.

Measures

Psychopathology was assessed through the self-rating Beck Depression Inventory [BDI (Beck *et al.*, 1961]), the expert-rating Hamilton Rating Scale for Depression (HRSD, 21-item version [Hamilton, 1967]) and the Global Assessment of Functioning Scale [GAF (American Psychoatric Association, 1994]). To assess general information about patients and the treatment process, a customized version of the German basic documentation system (BADO [Cording *et al.*, 1995]), that took the special needs of inpatient depression care into account, was used.

Statistical data analysis

Latent class analyses were conducted to identify substantially meaningful groups of patients that received similar interventions and intervention combinations during inpatient treatment. The decision on the number of latent classes was based on several criteria. The Schwarz (Bayesian) Information Criterion (BIC) as well as Akaike's Information Criterion (AIC) were used as statistical indices considering both model fit and parsimony (Nylund *et al.*, 2007). Their absolute values are rarely informative, but they play a central role in comparing competing models. Both indices increase with misfit and model complexity, thus, lower values are preferred. They are often used to guide model selection in mixture modeling, with a number of simulation studies suggesting that the BIC is the best sole indicator for class enumeration (Nylund *et al.*, 2007; Tein *et al.*, 2013; Yang, 2006). In addition, each model with k classes was directly tested against a model with $k - 1$ classes via the Vuong–Lo–Mendell–Rubin likelihood ratio test and the Lo–Mendell–Rubin adjusted likelihood ratio test. Both tests compare the improvement in fit between neighboring class models and provide a p value that can be used to determine if there is a statistically significant improvement in fit by the inclusion of one more class (Nylund *et al.*, 2007).This procedure was used with an increasing number of k, until the first statistically non-significant (p above 0.05) finding. Additionally, the accuracy of classification (entropy) was considered. The entropy is calculated from the probabilities of assigning patients to classes and can be handled as an average measure of the certainty or unambiguousness of this assignment. A higher value of entropy indicates that the latent classes are better discriminated, and usually a value above 0.80 is considered acceptable. Although informative as an additional criterion, a simulation study showed that entropy values alone poorly identify the correct number of classes (Tein *et al.*, 2013). Further, a graphical tool (Class Evolution Tree) was used to systematically address

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the issue of model selection in cases where statistical criteria are equivocal (Kriston *et al.*, 2011). For further analyses, patients were allocated to the class to which they were assigned with the highest probability (so called "most likely class" approach). In order to ensure that substantially uncertain assignments do not introduce bias to the results, sensitivity analyses were conducted including only patients that could be assigned to a certain class with a probability of over 50%.

After determining the number of classes, comparative analyses were performed using univariate and multivariate methods, such as χ^2-tests, *t*-tests, and logistic regression, to detect and describe differences in the composition of the identified classes with regard to demographic (e.g. age, sex, level of education, family status, occupational status) and clinical (e.g. severity of depression at admission, diagnosis, duration of illness, mental and somatic comorbidity) patient characteristics. Finally, associations between treatment outcome and receiving a class of interventions were investigated in linear or logistic regression models (depending on the outcome). In these analyses, specific definitions of treatment outcome were applied: duration of inpatient stay, response (defined as at least 50% decrease from baseline score in HRSD), remission (HRSD ≤ seven points), absolute HRSD and GAF scores at discharge, and absolute change of HRSD and BDI. We adjusted all analyses for the design of the primary study to statistically control for design effects (see later). To account for the possibility that treatment outcome in a certain class depends on the casemix of patients, we conducted sensitivity analyses that statistically adjusted for the influence all demographic and clinical variables.

Data preparation

First, variables from the BADO were examined to identify optimal indicators to describe treatment strategies during inpatient stay. Variables were chosen for further analyses based on their completeness, distribution, and relevant content. Twenty-one indicators were included: treatment with a SSRI, a TCA, a modern antidepressant (mod AD [venlafaxine, mirtazapine, reboxetine]), a monoamine-oxidase-inhibitor (MAO), a neuroleptic, a tranquilizer, a mood stabilizer, individual psychotherapy, electroconvulsive therapy, light therapy, relaxation, psycho-education, symptom management, cognitive training, social competence training, social counseling, occupational therapy, physical therapy, music therapy, art therapy, sport therapy and practical skills training.

Second, intraclass correlation coefficients (ICCs) were estimated to explore whether specific interventions were more likely to be used in specific hospitals. ICCs varied between 0.000 (standard error [SE] = 0.002) for the use of a modern antidepressant and 0.651 (SE = 0.256) for electroconvulsive therapy, indicating a great variation across hospitals regarding the administration of specific treatments. However, hospital-level variation could not be sufficiently modeled in the present study due to the limited number of hospitals and the computational complexity of the statistical approach. But, it was possible to account for the possible effects of the intervention tested in the primary study (see earlier), which may have affected not only quality assurance practices but also single treatments and treatment combinations. All analyses were statistically controlled for intervention effects (experimental versus control hospital), time effects (baseline versus follow-up assessment), as well as the interaction of both. This was realized by defining a model for the latent class analyses that estimated effects of the three factors (intervention, time, interaction) on *indicators variables* (treatments) and the *latent classes* (treatment combination pattern) at the same time.

Analyses were performed using PASW Statistics for Windows, version 18.0, and Mplus 6.1 (L. Muthén and Muthén, 2011).

Results

In total, data were collected from 2133 patients constituting the sample for the present study. The mean age of the sample was 51.2 years (standard deviation [SD] = 15.8), and 63.1% of the patients were female. Around half of the patients were married or living with a partner (53.0%); 87.5% had German as first language. Every second patient had nine or less years of school education (52.7%). The average level of depression at admission was high according to self-ratings (BDI, mean [M] = 27.9, SD = 12.0) and moderate to severe according to expert ratings (HRSD, M = 23.8, SD = 9.1).

The Vuong–Lo–Mendell–Rubin likelihood ratio test and the Lo–Mendell–Rubin adjusted likelihood ratio test indicated a best solution with two classes (see Table 1). Yet, both the AIC and the BIC decreased with a growing number of classes, indicating that solutions with more than two classes provided a better data fit. A solution with a higher number of classes was also suggested by the entropy values that tended to increase with increasing number of classes and first reached the required criterion (above 0.80) in a solution with eight classes. The BIC indicated a solution with eight classes, whereas the AIC indicated a solution with 10 classes. As simulation studies comparing both of these statistical criteria showed superiority of the BIC over the AIC (Nylund *et al.*, 2007; Tein

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Table 1. Model fit indices for latent class analyses

Model	LL	nfp	AIC	BIC	pVLMRLRT	pLMRaLRT	Entropy
1 class	–23884.981	88	47945.962	48444.507	NA	NA	NA
2 classes	–23118.700	114	46465.400	47111.242	<0.001	<0.001	0.709
3 classes	–22889.880	140	46059.761	46852.901	0.743	0.743	0.769
4 classes	–22657.090	166	45646.181	46586.618	0.760	0.760	0.772
5 classes	–22486.187	192	45356.374	46444.108	0.762	0.763	0.783
6 classes	–22344.510	218	45125.019	46360.051	0.426	0.426	0.788
7 classes	–22219.577	244	44927.153	46309.482	0.231	0.233	0.755
8 classes	–22098.805	270	44737.610	*46267.237*	0.364	0.366	*0.802*
9 classes	–22001.351	296	44594.702	46271.627	0.679	0.680	*0.811*
10 classes	–21923.167	322	*44490.334*	46314.556	0.236	0.240	*0.843*

Note: LL, loglikelihood; nfp, number of free parameters; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; pVLMRLRT, *p*-value of the Vuong–Lo–Mendell–Rubin likelihood ratio test; pLMRaLRT, *p*-value of the Lo–Mendell–Rubin adjusted likelihood ratio test; NA, not applicable; italic typeface refers to preferred solution according to specific criterion.

et al., 2013; Yang, 2006), a solution with eight classes was preferred for all further analysis (see Table 1). In order to obtain additional information for deciding between the two- and eight-class solutions, we prepared a Class Evolution Tree (Kriston *et al.*, 2011). This showed that the two-class solution consisted of a "high intensity" and a "low intensity" treatment class that split up in eight classes of more distinct and clinically more meaningful versions of "high" and "low" intensity treatments in the eight-class solution. This reinforced the decision for eight instead of two classes from a clinical point of view.

Taking relative frequencies of received interventions and the total number of interventions that was received within a certain class into account we assigned a label to each treatment combination class. Classes differed strongly concerning types of received interventions (e.g. use of SSRI varied between 40% and 100% between classes) as did the average number of received interventions (3.0 to 9.8). Two classes were identified that were characterized by a high number of received interventions but differed in the use of different pharmacological interventions ("high intensity innovative" and "high intensity traditional"), whereas a third class was characterized by very low total treatment intensity ("low intensity"). Two further classes were characterized by the use of either modern antidepressants or SSRI as pharmacological agents combined with some further interventions ("standard mod AD" and "standard SSRI"), whereas another class was dominated by the use of older antidepressants such as TCA ("standard TCA"). Another high intensity class was characterized by the use different of social psychiatric and psychological interventions like social counseling or daily life training ("high intensity psychosocial"), and the last class was characterized by the relatively frequent administration of electroconvulsive therapy and mood stabilizers ("somatic"). A detailed description of each class (treatment combination) is reported in Table 2. Additional sensitivity analyses that were conducted including only patients who could be assigned to a certain class with a probability of over 50% showed very similar results.

Each of the 10 hospitals used various classes of treatment combinations and each treatment class was found in more than one hospital, with most hospitals using four to five main strategies of treatment combinations. We ran an additional analysis to definitely rule out that the solution with 10 instead of eight classes represented the 10 hospitals of our sample exactly (i.e. that each hospital administered its own specific treatment combination). The results showed that even though treatment classes were unequally distributed across hospitals, the treatment combinations could not be unambiguously allocated to single hospitals.

Demographic and clinical patient characteristics differed strongly between classes. For example, patients with bipolar depression had a higher chance to receive the treatment pattern labelled "somatic" that was characterized through the use of mood stabilizers and electroconvulsive therapy (see Tables 3 and 4).

Rates of response ranged from 68.4% in the "low intensity" class to 86.8% in the "high intensity psychosocial" class. Remission rates were lowest in the "low intensity" class (49.3%) and highest in the "high intensity innovative" class (61.4%). After adjusting for the casemix of patients, differences in response and remission rates did

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Table 2. Description of the identified latent treatment combination classes

Intervention (Kramers V)[1]	Class 1 $n = 487$ (22.8%)	Class2 $n = 311$ (14.6%)	Class 3 $n = 258$ (12.2%)	Class 4 $n = 260$ (12.1%)	Class 5 $n = 248$ (11.6%)	Class 6 $n = 205$ (9.6%)	Class 7 $n = 187$ (8.8%)	Class 8 $n = 177$ (8.3%)
Treatment with mod AD (0.696)	100%	4.5%	0%	46.5%	43.5%	57.6%	38.5%	34.5%
Treatment with SSRI (0.691)	4.7%	1.0%	100%	43.5%	10.9%	29.8%	44.4%	14.7%
Occupational therapy (0.591)	95.5%	95.8%	91.5%	96.5%	29.8%	92.7%	89.8%	81.9%
Treatment with TCA (0.562)	0%	69.5%	6.2%	21.9%	13.3%	14.6%	51.9%	24.3%
Sport therapy (0.552)	80.7%	80.1%	69.0%	88.5%	7.7%	52.7%	98.9%	52.0%
Psychoeducation (0.495)	41.5%	38.3%	46.5%	71.9%	10.5%	0.5%	89.3%	35.6%
Music therapy (0.493)	24.2%	20.3%	26.0%	79.2%	0.4%	10.2%	15.5%	42.4%
Practical skills training (0.490)	29.4%	9.6%	24.8%	18.8%	16.9%	6.8%	15.0%	95.5%
Relaxation (0.472)	43.1%	50.2%	56.6%	24.6%	14.5%	19.5%	88.2%	87.0%
Cognitive training (0.462)	21.4%	21.9%	20.5%	38.5%	9.7%	3.9%	5.9%	80.8%
Electroconvulsive therapy (0.448)	1.0%	0%	0.4%	3.8%	3.6%	32.7%	1.1%	1.1%
Physical therapy (0.417)	26.7%	25.1%	36.0%	55.4%	7.7%	80.0%	50.8%	57.6%
Symptom management (0.399)	1.6%	0%	1.6%	28.5%	1.6%	0%	8.0%	4.0%
Social counselling (0.388)	52.2%	43.7%	59.6%	81.5%	17.7%	25.4%	32.6%	74.0%
Light therapy (0.376)	10.9%	4.8%	9.3%	1.2%	1.6%	1.0%	34.2%	35.6%
Social competence training (0.376)	7.4%	7.7%	10.5%	35.4%	4.0%	2.0%	21.9%	43.5%
Individual psychotherapy (0.354)	65.1%	54.0%	67.4%	83.1%	34.7%	42.9%	84.0%	88.7%
Art therapy (0.350)	22.0%	13.8%	26.0%	47.7%	0.4%	17.1%	50.8%	17.5%
Treatment with tranquilizers (0.330)	41.5%	20.3%	26.4%	7.3%	35.1%	7.3%	48.1%	51.4%
Treatment with MAO (0.295)	0.2%	0%	0%	0.8%	2.4%	6.8%	0%	15.8%
Treatment with neuroleptics (0.227)	49.5%	37.6%	43.4%	19.2%	23.4%	35.6%	52.9%	39.0%
Treatment with mood stabilizers (0.196)	11.5%	12.5%	12.4%	18.1%	5.6%	28.8%	4.8%	7.3%
Total number of interventions received[2]	7.3±1.8	6.2±1.9	7.2±1.9	9.1±2.1	3.0±1.5	5.7±1.7	9.3±2.0	9.8±2.0
Label	“standard mod AD”	“standard TCA”	“standard SSRI”	“high intensity innovative”	“low intensity”	“somatic”	“high intensity traditional”	“high intensity psychosocial”

[1]Indicators are ordered according to their discriminatory power among the different classes as measured by Kramers V.
[2]Variable not included in the latent class analyses, reported here only for description.
Note: Shading: dark grey = more than 75% of the patients received the intervention; light grey = more than 50% of the patients received the intervention; dotted lines = more than 25% of the patients received the intervention.

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Table 3. Associations between demographic characteristics and treatment combination classes

Class	Class 1 $n = 487$ "standard mod AD"	Class 2 $n = 311$ "standard TCA"	Class 3 $n = 260$ "standard SSRI"	Class 4 $n = 258$ "high intensity innovative"	Class 5 $n = 248$ "low intensity"	Class 6 $n = 205$ "somatic"	Class 7 $n = 187$ "high intensity traditional"	Class 8 $n = 177$ "high intensity psychosocial"	p Value
Sex[1]									0.073
female	65.2%	62.9%	64.2%	65.9%	60.9%	53.2%	67.7%	62.1%	
Age[2]									<0.001
M (SD)	56.1 (16.0)	50.1 (14.4)	45.9 (14.6)	48.5 (14.7)	51.3 (18.1)	51.6 (16.0)	48.7 (13.1)	53.0 (15.6)	
Family status[1]									<0.001
Single	14.2%	18.1%	30.0%	21.0%	21.4%	18.1%	16.6%	16.4%	
Married/living with a partner	51.5%	56.1%	45.8%	55.3%	48.8%	56.9%	60.4%	52.0%	
Divorced/separated	15.3%	15.2%	18.8%	12.8%	15.3%	16.7%	18.2%	18.6%	
Widowed	19.0%	10.6%	5.4%	10.9%	14.5%	8.3%	4.8%	13.0%	
Education[1]									<0.001
Low	63.0%	56.4%	31.2%	52.7%	57.3%	49.0%	53.1%	48.6%	
Middle	21.8%	26.5%	29.2%	26.5%	20.9%	24.0%	28.5%	23.2%	
High	15.3%	17.1%	39.6%	20.8%	21.8%	27.0%	18.4%	28.2%	
Occupation[1]									<0.001
Yes	30.8%	40.2%	55.8%	48.1%	33.5%	37.1%	48.1%	33.9%	
Hospital[1]									<0.001
1	9.0%	13.8%	13.8%	8.9%	17.3%	1.0%	12.3%	2.8%	
2	6.8%	5.8%	1.5%	8.5%	29.4%	0.0%	0.5%	69.5%	
3	21.4%	9.3%	6.2%	10.9%	6.5%	1.5%	9.6%	6.8%	
4	14.0%	11.3%	0.8%	12.0%	4.8%	2.4%	0.0%	2.3%	
5	2.7%	2.3%	0.0%	3.9%	2.8%	76.6%	0.0%	0.6%	
6	21.4%	23.5%	0.0%	7.8%	18.1%	6.8%	0.5%	5.6%	
7	8.6%	12.5%	0.0%	21.3%	6.0%	7.8%	3.7%	5.6%	
8	6.0%	3.5%	0.0%	15.1%	4.0%	2.9%	0.0%	2.8%	
9	5.1%	5.8%	4.2%	8.5%	4.4%	0.0%	67.9%	2.8%	
10	5.1%	12.2%	73.5%	3.1%	6.5%	1.0%	5.3%	1.1%	
Mother tongue[1]									0.022
German	87.5%	83.3%	88.8%	88.0%	85.9%	90.2%	89.8%	89.3%	

Note: *n*, number of patients in class; *p*, level of significance; *M*, mean; SD, standard deviation.
[1]Presented *p*-values are based on χ^2-test.
[2]Presented *p*-value is based on *t*-test.

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Table 4. Associations between clinical characteristics and treatment combination classes

	Class 1 $n = 487$ "standard mod AD"	Class 2 $n = 311$ "standard TCA"	Class 3 $n = 260$ "standard SSRI"	Class 4 $n = 258$ "high intensity innovative"	Class 5 $n = 248$ "low intensity"	Class 6 $n = 205$ "somatic"	Class 7 $n = 187$ "high intensity traditional"	Class 8 $n = 177$ "high intensity psychosocial"	p Value
Diagnosis at admission[1]									<0.001
Unipolar	48.9%	42.4%	33.8%	44.6%	36.7%	42.0%	42.2%	29.9%	
Bipolar	5.3%	3.5%	8.1%	5.4%	2.8%	13.7%	3.2%	5.6%	
Recurrent	38.6%	41.5%	49.6%	39.5%	37.1%	37.1%	48.1%	55.4%	
Dysthymia	0.8%	0.6%	1.2%	1.6%	0.4%	2.9%	1.1%	0.6%	
Adjustment disorder	6.4%	11.9%	7.3%	8.9%	23.0%	4.4%	5.3%	8.5%	
Mental comorbidity[1]									<0.001
Yes	22.2%	29.3%	44.6%	29.1%	27.0%	33.7%	27.8%	22.6%	
Somatic comorbidity[1]									<0.001
Yes	37.6%	28.0%	44.2%	25.6%	36.3%	36.1%	20.3%	47.5%	
Previous inpatient stay[1]									<0.001
Yes	55.9%	55.0%	52.3%	51.9%	51.2%	69.3%	55.1%	67.8%	
HRSD at admission[2]									<0.001
M (SD)	23.0 (8.3)	22.0 (7.4)	22.7 (6.7)	22.6 (9.1)	23.1 (10.2)	22.2 (8.8)	26.2 (8.0)	31.6 (10.7)	
BDI at admission[2]									
M (SD)	27.1 (11.1)	26.4 (11.9)	28.4 (10.1)	26.0 (10.6)	25.8 (13.3)	26.7 (11.1)	28.1 (12.0)	37.7 (13.5)	
GAF at admission[2]									<0.001
M (SD)	45.6 (12.5)	46.9 (12.4)	43.0 (13.2)	46.6 (13.5)	46.1 (16.0)	45.7(12.9)	41.0 (13.6)	41.2 (12.6)	
Family history of mental disorder[1]									<0.001
Yes	23.9%	25.6%	43.3%	27.8%	32.7%	31.7%	36.7%	52.0%	

Note: *n*, number of patients in class; *p*, level of significance; *M*, mean; SD, standard deviation; HRSD, Hamilton Rating Scale for Depression; BDI, Becks Depression Inventory; GAF, Global Assessment of Functioning scale.
[1]Presented *p*-values are based on χ^2-test.
[2]Presented *p*-values are based on *t*-test.

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Table 5. Associations between outcome and treatment combination classes

Outcome	Class 1 $n = 487$ "standard mod AD"	Class 2 $n = 311$ "standard TCA"	Class 3 $n = 260$ "standard SSRI"	Class 4 $n = 258$ "high intensity innovative"	Class 5 $n = 248$ "low intensity"	Class 6 $n = 205$ "somatic"	Class 7 $n = 187$ "high intensity traditional"	Class 8 $n = 177$ "high intensity psychosocial"	p^*	p^{**}	Part. Eta^2
Length of stay (days)[1]									<0.001	<0.001	0.093
M (95% CI)	41.0 (38.1–43.9)	38.5 (34.8–42.2)	68.1 (63.8–72.4)	41.2 (37.1–45.3)	23.6 (19.5–27.7)	51.7 (46.8–56.6)	75.6 (70.7–80.5)	49.7 (44.6–54.8)			
Responded[2,3]									<0.001	0.361	0.017
% (95% CI)	76.9 (73.0–80.8)	79.7 (75.0–84.5)	85.1 (78.9–91.4)	77.2 (72.0–82.5)	68.4 (62.2–74.6)	81.4 (76.1–86.8)	83.0 (77.4–88.5)	86.6 (81.6–91.7)			
Remitted[2,4]									<0.001	0.309	0.011
% (95% CI)	53.5 (49.0–58.1)	64.7 (59.1–70.3)	61.4 (52.9–70.0)	58.2 (52.0–64.4)	49.3 (42.8–56.0)	58.0 (51.2–64.8)	54.9 (47.6–62.2)	43.3 (36.0–50.7)			
HRSD at discharge[1]									<0.001	0.001	0.037
M (95% CI)	7.7 (7.1–8.3)	6.4 (8.8–10.4)	6.2 (5.0–7.4)	7.3 (6.5–8.1)	9.6 (8.8–10.4)	7.7 (6.7–8.7)	7.3 (6.3–8.3)	8.2 (7.2–9.2)			
Change HRSD[1]									<0.001	0.001	0.037
M (95% CI)	15.8 (15.0–16.6)	15.9 (14.9–16.9)	16.0 (14.4–16.6)	15.8 (14.6–17.0)	13.4 (12.2–14.6)	15.1 (13.7–16.5)	18.1 (16.7–19.5)	22.8 (21.4–24.2)			
BDI at discharge[1]									0.039	<0.001	0.048
M (95% CI)	12.4 (11.4–13.4)	11.5 (10.1–12.9)	10.2 (8.8–11.6)	11.1 (9.7–12.5)	12.2 (10.6–13.8)	13.3 (11.7–14.9)	9.7 (8.1–11.3)	11.0 (9.4–12.6)			
GAF at discharge[1]									0.016	0.022	0.025
M (95% CI)	69.0 (67.8–70.2)	70.7 (69.1–72.3)	71.7 (69.9–73.5)	71.0 (69.2–72.8)	68.4 (66.6–70.2)	69.9 (67.9–71.9)	67.8 (65.6–70.0)	69.7 (67.5–71.9)			

Note: *n*, number of patients in class; *p*, level of significance; *M*, mean; CI, confidence interval; HRSD, Hamilton Rating Scale for Depression; BDI, Becks Depression Inventory; GAF, Global Assessment of Functioning scale.

*All values are adjusted for phase, group and interaction of phase and group.

**All values are adjusted for phase, group and interaction of phase and group, and additionally for all demographic and clinical variables reported in Tables 3 and 4

[1]Presented *p*-values are based on linear regressions.

[2]Presented *p*-values are based on logistic regressions.

[3]Defined as at least 50% decrease from baseline score in HRSD.

[4]Defined as HRSD ≤ seven points at discharge; part. Eta^2 = additional explained variance of the factor "class" after adjusting for phase, group, interaction of phase and group, and all demographic and clinical variables (in case of logistic regression the difference in Nagelkerkes pseudo R^2 statistics is reported as an estimate of explained variation by the factor "class").

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no longer reach statistical significance, yet differences were still found for the absolute level of depression, level of functioning, and duration of inpatient stay. The correlation between classes and treatment outcome varied between 1% for remission and 9% for the duration of inpatient stay. A detailed description of treatment outcome in all classes can be found in Table 5.

Discussion

Eight different classes of inpatient depression treatment combinations could be identified through latent class analyses. Differences between the classes were shown regarding the combinations of different treatments and the total number of combined treatments. Our finding that different pharmacological interventions are frequently combined in routine depression care is in accordance with previous findings that reported the combination of antidepressants with antipsychotics, sedative-hypnotics, and other antidepressants as a common strategy in patients with depression (Barbui *et al.*, 2005; M. Bauer *et al.*, 2008; de la Gándara *et al.*, 2005; Mojtabai and Olfson, 2010).

Our findings further highlight that the chosen treatment combinations vary as a function of patient characteristics, leading to the conclusion that differential indication strategies were used. Apart from patient characteristics the individual hospital influenced the choice of treatments, which is in accordance with previous findings that reported that the selection of antidepressants is influenced by physician- and patient-related factors (Bauer *et al.*, 2008; Sleath and Shih, 2003; Zimmermann *et al.*, 2004).

Treatment outcome was found to differ between the different treatment classes. However, it should be noted that the relation between treatment class and outcome is purely correlative and should not be interpreted causally. The rates of responders were found to be higher in classes that received a higher number of interventions compared to classes that received fewer interventions (87% responders in the "high intensity psychosocial" class that received 9.8 ± 2.0 interventions on average compared with a response rate of 68% in the "low intensity" class that received 3.0 ± 1.5 interventions on average). This correlative association between the number of interventions and treatment outcome conflicts with previous findings that report no correlation between polypharmacy and efficacy (Glezer *et al.*, 2009). Even though our findings indicate a dose–response relationship with a higher number of interventions leading to more favorable outcomes, another explanation of this correlative relationship could be that each patient received a tailored combination of interventions. The hypothesis of (optimal) treatment choices for each individual patient instead of generally more or less effective treatment combinations may at least partly be supported by the finding that patient characteristics differed between classes. Additionally, the results of the casemix adjusted analyses indicated that some of the variance in treatment outcome can be explained through differences in patient characteristics. Yet, even after controlling for the casemix small but substantial differences in treatment outcome were found between classes. A possible explanation for the rather low explanatory power of patient characteristics (casemix) for the association between treatment class and outcome could be the lack of information on crucial patient characteristics that were not assessed sufficiently. For example detailed information on the type of somatic and/or mental comorbidity are likely to have an important effect on the use of different pharmacological agents.

Another limitation of the presented results is the ambiguity of the statistical indices that did not clearly agree on the number of classes in the best model. Thus, the preferred model with eight treatment classes was selected by including also clinical consideration. Within the statistically acceptable models, a solution with a higher number of classes was likely to provide more clinical information (leading to favoring the eight-class solution over the two-class solution), and a solution with a lower number of classes was likely to enhance interpretability (leading to favoring the eight-class solution over the 10-class solution). This introduced some subjectivity in the model selection process. However, considering that statistical selection criteria are likely to disagree on the best model in latent class analyses, integrating the assessment of interpretability and practical applicability in model selection decisions is recommended (Bauer and Curran, 2003; Jung and Wickrama, 2008; Muthén and Muthén, 2000).

One major limitation of the presented secondary analysis is that no data on the level of physicians or specific wards were available. Differences between hospitals indicated that the choice of treatment combinations seemed to vary not only as a function of patient characteristics but also as a function of the institution delivering the treatment. Previous research has shown that a number of factors can influence antidepressant selection by psychiatrists, such as specific side effects, comorbid mental disorders, and the presence of specific clinical symptoms (Zimmermann *et al.*, 2004). Thus, in order to further examine the relationship between patient characteristics and received treatment further research on the interdependent relations between patients, caregivers, and setting is needed.

The treatment classes identified in this secondary analysis are based on data from over 2000 depressed routine

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care inpatients treated in 10 different hospitals, thus providing a valuable basis for the identification of treatment combinations. Yet, as latent class analysis depends considerably on the composition of the underlying population and choice of variables, a replication of these exploratory findings in a broader range of hospitals is desirable to eliminate possible confounders that are specific to the sample examined in this study. It should be noted that the estimation of ICCs with binary data that was used to estimate the multi-level character of our data is challenging and depends heavily on the marginal distributions (Eldridge *et al.*, 2009; Wu *et al.*, 2012).

Another important limitation to the findings is that due to the low number of hospitals we were unable to investigate the association of hospital characteristics (e.g. location, type, size) and different intervention classes. Particularly concerning the substantial differences in the distribution of the intervention classes across hospitals, this issue deserves further research attention utilizing data from more hospitals. For example, results showed that some treatment classes seem to be highly specific for certain hospitals, e.g. "standard SSRI" or "high intensity psychosocial" treatments that were administered mainly in one hospital each. Other treatment strategies, such as "high intensity innovative" care was found as a common treatment strategy in more than one hospital. Further studies are therefore needed to differentiate better between treatment strategies that are specific to certain hospitals and strategies that are commonly used across a broader range of hospitals.

Conclusions

Our study provides a detailed yet parsimonious model of inpatient care of depression. Modeling component combinations of a complex intervention with means of latent class analysis successfully reduced the complexity of routine health care to fairly distinct classes.

The presented inpatient treatment combinations may provide relevant information for health care professionals on what actually happens in psychiatric hospitals (i.e. which components are administered in which combination), what may lead to a re-evaluation and optimization of treatment strategies and may also serve as a starting point for cost-effectiveness research, thus providing relevant information for health care organizations and guideline developers. Our results indicate that each patient receives a tailored combination of interventions in routine care. Nearly all patients received a specific antidepressant pharmacological agent and individual psychotherapy which is in accordance with current guidelines for depression (DGPPN *et al.*, 2009). The use of current best evidence in making decisions for individual patients is in accordance with principles of evidence-based medicine (Sackett *et al.*, 1996). Nevertheless, beside the precise tailoring of treatment combinations, our results indicate small but substantial differences between treatment combinations concerning outcome that cannot be explained purely by the casemix of the sample, suggesting that especially high intensity treatment combinations may lead to more favorable outcomes. Yet, these high intensity combinations were also associated with longer treatment duration and may therefore raise questions regarding cost-effectiveness of inpatient care.

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Declaration of interest statement

All authors declare that they have no conflicts of interest.

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